Appl. No. 09/808,706
Amdt. dated August 13, 2003
Reply to Office Action of February 13, 2003

REMARKS/ARGUMENTS

Claims 1-8 and 29-51 are pending. Claim 1 has been amended to correct an informality. New claims 29-51 have been added. No new matter has been introduced.

Claims 1-8 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Atwood (USPN 5,766,889), in view of Berndt (USPN 6,080,574).

Applicants respectfully submit that independent claims 1and 29 are patentable over Atwood (USPN 5,766,889) and Berndt (USPN 6,080,574).

Atwood discloses a method for determining an unknown starting molar concentration of target nucleic acid in a sample reaction mixture by performing PCR on the sample, recording a growth curve, and performing successive approximations to obtain a best fit (e.g., using a least squares algorithm) between a calculated theoretical growth curve and the measured growth curve of the sample. Atwood does not teach or suggest the steps of determining a derivative of the growth curve or determining a threshold cycle number or threshold time value associated with a characteristic of the derivative.

Berndt discloses an optical blood culture sensor for detecting microorganism growth by simultaneously measuring the fluorescent intensity of a fluorophore dependent upon oxygen concentration in the container and the optical transmission of a chromophore that depends upon carbon dioxide concentration. There are three references in Berndt to first derivatives of microorganism growth curves.

Figs. 8 and 11 of Berndt (discussed at column 7, lines 13-16 and lines 29-33, respectively)) are plots showing first derivatives of the signals in Figs. 7 and 10, illustrating that oxygen consumption and carbon dioxide production are separable.

Fig. 14 (discussed at column 7, lines 53-63) shows the first derivative of a growth curve (perhaps that of Fig. 8) and identifies six characteristic features: the times of occurrence of O_2 and CO_2 appearance, the duration (FWHM) of these effects, and the strength (amplitude) of both effects. The Berndt patent goes on to say (col. 7, lines 58-63):

> Applicant has found that by compiling a set of these six characteristic parameters for each sample vial and comparing the set with the corresponding data base that has

been generated using known samples at an earlier time, a presumptive microorganism identification can be achieved.

Berndt uses his first derivatives to identify the microorganism, not to quantify the culture growth. Further, the "characteristics" of the first derivative identified as useful in the method of Berndt, i.e., FWHM and amplitude, are not those used by Applicants of the instant invention (time or cycle number of positive peak, negative peak, or zero crossing). Note also that Berndt does not use his "characteristics" individually, but combines them into a set of six. Finally, Berndt is completely silent as to the use of higher order derivatives.

Berndt thus discloses measuring a signal, deriving a growth curve, calculating a first derivative and identifying a set of characteristics. Berndt does not disclose amplifying nucleic acid sequences, calculating n^{th} order derivatives, identifying a characteristic of the derivative (positive, negative or zero crossing), and determining a cycle number or time value associated with the characteristic.

I. The Combination of References Does Not Lead to the Claimed Invention

Applicants request reversal of the rejection on the basis that the Examiner has not properly considered the factors set forth in *Graham v. John Deere*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966) to arrive at her conclusion of obviousness. In fact, when properly applied, the *Graham* factors lead inexorably to a conclusion of non-obviousness for the claimed invention.

As set forth in M.P.E.P. § 2141, when applying 35 U.S.C. § 103, the following tenets of patent law must be adhered to:

(A) The claimed invention must be considered as a whole;

(B) The references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;

(C) The references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and

(D) Reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 U.S.P.Q. 182, 187 n.5 (Fed. Cir. 1986).

Atwood does not teach or suggest the steps of determining a derivative of the growth curve or determining a threshold cycle number or threshold time value associated with a characteristic of the derivative. Berndt does not teach or suggest amplifying nucleic acid sequences, calculating n^{th} order derivatives, and determining a threshold cycle number or time of amplification associated with a characteristic of the derivative. Together the references do not fairly teach or suggest the use of a characteristic of a derivative, as defined by Applicants, in a process for determining threshold cycle number or time value in a nucleic acid amplification reaction.

To arrive at the conclusion of combined reference obviousness, most of the teachings of, and, in fact, the entire invention of Atwood must be ignored, namely the curve fitting method. Atwood is dismissed by the Examiner after providing the steps of amplifying, measuring, and generating a growth curve. Berndt is then improperly invoked to provide the additional steps of calculating a derivative of a growth curve and identifying a characteristic of the derivative, although the characteristics of Berndt are not those of the current invention nor are the characteristics used individually. Finally, the Examiner attempts to revert to Atwood for determining a threshold cycle number from the characteristics of Berndt. This reverse engineering of the claimed invention is only possible in hindsight and should not be the basis of an obviousness rejection.

II. Lack of Motivation to Combine References

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 U.S.P.Q.2d 1430, 1432 (Fed. Cir. 1990). Prior art references in combination do not make an invention obvious unless something in the prior art references would suggest the advantage to be derived from combining their teachings. *In re Sernaker*, 702 F.2d 989, 217 U.S.P.Q. 1, 6 (Fed. Cir. 1983).

There is nothing in either the Atwood or Berndt references that suggests an advantage to be derived by combining their teachings, nor would one skilled in the art have any motivation to even attempt to do so. Constructing a set of six characteristics of a growth curve as taught by Berndt would serve no useful purpose in performing Atwood's best-fit method. Atwood's method depends on performing successive approximations to obtain a best fit between a calculated theoretical growth curve and the measured growth curve of a sample. The Berndt

method of determining a set of characteristics of either the calculated theoretical growth curve or the measured growth curve would not help accomplish the best fit.

III. Hindsight Reconstruction

The motivation to combine references can not come from the invention itself. *Heidelberger Druckmaschinen AG v. Hantscho Commercial Products, Inc.*, 21 F.3d 1068, 30 U.S.P.Q.2d 1377 (Fed. Cir. 1993). Here, not only is the combination not suggested by either reference, but the references must themselves be modified to arrive at the claimed invention. This is not appropriate under *Graham*. Even if combined, the references do not teach the claimed invention.

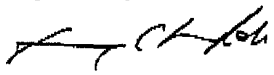
The dependent claims incorporate all of the subject matter of their respective independent claims 1 and 29 and add further limitations, which makes them *a fortiori* patentable over the references. In particular, Applicants note that the cited art is completely silent as to the use of second order derivatives. Therefore, Applicants submit that all claims 1-8 and 29-51 define patentably over the cited art.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,



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